REMARKS

Claims 1-65, 234-331, 466-509 are all the claims pending in the application. Claims 1-65, 234-331 and 466-509 are all the claims pending in the present Application.

The Applicants traverse the requirement for a substitute oath and the rejection of pending claims based on prior art and request reconsideration.

I. Formal Matters

In ¶ 2, the Examiner has found the oath to be defective because the present declaration has citizenship listed as "Israeli". 37 C.F.R. § 1.63(a)(3) requires that the oath must "identify the country of citizenship". The Applicants respectfully submit that they have met this requirement clearly, unambiguously and unequivocally. There is no specific requirement in the law or in rules of practice as to the explicit wording that is required in identifying country of citizenship. It is commonplace to state correctly that "a person is citizen of Israel" or as "a person has Israeli citizenship". Both these statements clearly identify Israel as being the country of citizenship, meeting the requirements of 37 C.F.R. § 1.63(a)(3). Clearly, the Examiner is not believed to be alleging that the country of citizenship is ambiguous, because there is believed to be absolutely no likelihood of confusion with any other country. If on the other hand, the Examiner requires a specific wording, he is requested to provide support for his position. Requiring the Applicants to locate all the international inventors (as in the present case) and then

getting them to sign and resubmit the declaration because the Examiner prefers a specific wording is believed to be unduly burdensome.

Further, the address for each inventor listed on the declaration clearly states the country/state as "Israel". For all these reasons, the Examiner is requested to withdraw this objection.

II. Claim Objections

Claim 5 has been amended to overcome the Examiner's objection related to alleged misspelling of a term.

III. Section 112 rejections

Objected claim 246 has been amended to now correctly depend from claim 234.

IV. Prior art rejections

IV.A. Rejection of claims 1,18, 23-26, 41, 46-49, 274, 296, 506, 508 under 35 U.S.C. § 102(e) based on Barry

To anticipate a claim, every element and its corresponding limitation has to disclosed explicitly (or inherently in the cited references. MPEP § 2131 *citing Vardegall Bros. V. Union Carbide Co of California*, 814 F.2d 628 (Fed Cir. 1987). The identical invention must be shown in as complete a detail as is contained in the claims " *Id. citing Richardson v. Suzuki Motor Co.*, 868 F.2d 1226 (Fed. Cir. 19898).

Apparatus claims 1, 26, method claims 274, 296 and computer program product claims 506 and 508 are not anticipated by Barry because all the elements of these claims are not disclosed by Barry.

Barry discloses a database of available predefined treatment protocols for specific diseases, together with a database of therapeutic cross reactions, and a database of a patient history of reaction to different therapeutics. After inserting some general information of the patient and his/her medical status and history, the system will look in its database for all **predefined** appropriate therapies for this patient's disease, known reaction to previous medication, additional drugs taken, etc. and will rank them for their suitability.

Claims 1, 26, 274, 296, 506, 508, require at least a system model. "System model" as used in the present invention is clearly described on pages 74-75 of the present Specification. In these passages, it is clearly asserted that:

> Initially, system models are created. These include models to simulate all the relevant biological, clinical and pharmaceutical process 2.1. These models include mathematical models for processes that affect healthy cells as well as mathematical models for processes that affect cell populations with one or more diseases. In addition, a model of treatment effects 2.3 on each of these processes is created. The treatment effects include processes that are specific to individual treatment. Such a treatment may be based on the effects of a drug's process that affects the relevant cell population. Examples of these effects include interactions involving pharmacokinetic (PK), pharmacodynamics (PD), cytotoxic and cytostatics, or any other method of affecting cell biology and causing cell death, with associated biological processes.

> The combination of these models provides a detailed mathematical model of the overall bio-clinical scenario in a general sense or for a specific patient, together with the specific effects of a particular treatment.

While some of the details described above are claimed as improvements in dependant claims, clearly the "system model" in the independent claims 1, 26, 274, 296, 506, 508 refer to the overall bio-clinical scenario for a general patient as in claims 26, 296 and 508 and for a specific individual patient as in claims 1, 274 and 506. Barry does not disclose such a system model. Barry merely compiles a database of treatment protocols and then based on some patient information searches the database to extract relevant treatment protocols and further list, rank and describe them with helpful hints based on a knowledge base. There is absolutely no consideration of an overall bio-clinical scenario, and/or a mathematical model that creates an actual computer simulation of this bio-clinical scenario.

The Examine cites 8:5-20 of Barry for its teaching on the system model. In these passages Barry teaches:

> The system comprises a knowledge base of treatment regimes 21, which may be ranked for efficacy (e.g. by a panel of experts) or ranked according to system rules, a knowledge base of expert rules 22, a knowledge base of advisory information, a knowledge base of patient therapy history 24 and patient information 25. The knowledge bases and patient information 21-25 may be updated...

The above disclosure, by no means can be considered a "System model" as required by the present invention where an overall bio-clinical scenario for a patient is modeled, and its progression is simulated through its mathematical model.

Therefore claims 1, 26, 274, 296, 506, 508 are not anticipated by Barry at least because Barry does not disclose a system model as required by the present invention.

Additionally, claims 1, 274, 506, further require that the system model be modified based on individual patient information. Barry uses patient information merely to select a predefined treatment protocol. First, as described above, Barry does not disclose a system model as in the present invention. Even if the model in Barry is considered to be a system model, there is no teaching that the model is modified based on the characteristic information about the patient. Selection based on patient information, as in Barry, is completely different from modifying the overall bio-clinical scenario, through the manipulation of inherent biological parameters, based on patient information, as in the present invention.

Claims 18, 23-25 depend on claim 1. Therefore the arguments discussed above in relation to claim 1 are equally valid for claims 18, 23-25.

Claims 41, 46-49, depend on claim 26. Therefore the arguments discussed above in relation to claim 26 are equally valid for claims 41, 46 -49.

IV.B. Rejection of claims 1-3, 6-19, 22-28, 31-44, 55-65, 234, 235, 246-249, 260-263, 274-276, 279-294, 295-298, 301-314, 315-318, 321-327, 330-331, 466-467, 478-481, 494-495, 506-509 under 35 U.S.C. § 103(a) based on Barry in view of Fink

As discussed above in sub-section IVA, Barry is deficient at least to the extent that a system model as used in the present invention and modification of the system model based on patient information are not taught by Barry.

The Examiner alleges that Fink overcomes the above deficiency.

Fink at best provides an executable hierarchical models for biological systems . Fink suggest created and balanced the model for use in providing insight into phenomena at the cellular or sub-cellular level, as well as phenomena at the patient, organ and system level. However, a detailed look at the model clearly reveals that a realistic biological model is not contemplated. The model consists, at one of its levels, in cell pools that are regulated. Connections between cell pools are "regulated", e.g. the number of cells selected for movement from one cell type/state to the other, by the links that connect the "+" and "-" boxes on the links between the cell pools. These controlling items usually designate chemical level that either enhance or inhibit the cell transition between states. Each contributor to the transition function, or regulator, is weighed, usually with a value between 0 and 1. Initially the weight for each chemical influencing a transition is assigned equally. These weights are then adjusted when the model is balanced. This is at best a very simplistic representation and hardly a realistic biological model as used in the present invention. The type of constitutive equations encapsulating a biological mechanism are not even remotely suggested by Fink.

The Examiner admits that Barry does not disclose predicting the progression of a disease or using a realistic biological model. Citing 12:6713:4, the Examiner

asserts that Fink's model incorporates the effect of pharmacokinetic, pharmacodynamics, dosage, etc. This is believed to be a misinterpretation of Fink's teaching.

In the relevant passage, Fink suggests an example reflecting the reduction in levels of postaglandin levels brought about by the use of ibuprofen. All that Fink suggests is that the lowered level of postaglandin is simulated by the model and the model then determines the effect at the patient level. Based on this, Fink suggests that valuable information, including ranges, PK and PD for timings and dose implications may be observed and discovered. Therefore, Fink is merely suggesting observation of information based on the running of the model, which the user may then use to assess these various parameters. This is very different from realistic treatment models that model the effects of a treatment on the biological process as in the present invention (as recited in claim 2). It is even more significantly different from pharmacokinetic, pharmacodynamic, cytostatic, cytotoxic, and methods affecting cell biology and causing cell death, with associated biological processes as in the present invention (as recited in claim 7). Clearly, Fink is at best suggesting that through the knowledge of the clinical outcome of Ibuprofen and its direct affect on prostaglandin, Fink suggests that his invention can help in the exploration of further bio-pharmacological characteristics can be otbtained by extrapolation. While Fink uses the particular direct effect of a drug to extract information as to its mechanism of action and pharmaceutical properties, the current invention exploits all these and more data to produce a clinical prediction.

The Examiner cites to 12:49-55 of Fink in support of his position. In these passages, Fink merely suggests broadly that a drug treatment is modeled in terms of its impact on certain biological factors. For example, Fink suggests modeling the effect of a antimicrobial as a 30% cell loss. In addition, the Examiner refers to 3:30-40. However, in these passages Fink merely speculates on the realization that change in one system can have cascading effects on another that will in turn affect drug efficacy, side effect, and drug development profiles. A realistic model such as presented in the current invention must incorporate complex drug mechanisms, interactions, side effects, and pharmacological properties. By no means the simplistic % cell kill or the speculation of a cascading effect can suggest and substitute for a detailed and realistic modeling approach.

In apparent reference to claims 10-14, the examiner cites to 5:56-6:3. In this passage, Fink describes the use of certain graphical entities to manipulate data. These passages do not imply that a fitness function is used. Moreover, claims 10-14 cover the use of a fitness function as a user-specific parameter adjustment, to enable user-specific objective determination, and user-tailored optimal solutions. Specifically, as recited in claim 12 the user-specific parameters include patient survival, time to death, time to reach a specified disease stage (including cure), tumor load, pathogen load, cytotoxicity, side effects, quality of life, cost of treatment, pain, etc. All or some of these parameters can be graded according to a specific user's goal (depending on the treatment and the patient's preferences), thus enabling the best therapeutical intervention. For example, a scoring system

can be introuduced and score determined for each run/simulation so that a best score is obtained enabling the selection of an optimal treatment protocol. Fink does not suggest incorporating any of these user-specific parameters. The examiner is believed to be misinterpreting the current invention by implying that assigning a certain %ge of cell loss is equivalent to the kind of user-specific parameters that is contemplated in the present invention. Also, merely speculating that the systems can interact as in 3:30-40 of Fink is not believed to be a suggestion that user-specific treatment objective parameters are incorporated into the system model.

Further, the combined teachings of Barry/Fink is deficient in the sense that the system model as in the base claims 1, 26 with realistic bio-clinical model is not suggested. Further the realistic bio-clinical model is not modified as in claim 1,26. So the combined teaching of Barry/Fink needs to be modified at least to include making the model in Fink more realistic and the model's goal function being modified by user-specific parameters and further the selection of an optimal treatment protocol being based on the modified realistic bio-clinical system model. There is no explicit suggestion in Fink nor Barry to perform such a modification. Therefore the Examiner has not satisfied his burden to establish prima facie obviousness based on the combined teachings of Barry/Fink.

Further, if the teaching of Barry is modified to incorporate the teachings of Fink, the system disclosed by Barry will not function as it is designed to function. Barry includes knowledge bases that contain several predefined treatment models as well as knowledge bases that provide advise based on these predefined

treatment models. The selection from these "canned" treatment models and corresponding advise is based on information about the patient. However, if the information in these canned models are changed or "executed" (thereby making it dynamic) as in Fink, then the entire selection process will be wrong and the corresponding treatment advise would be erroneous. Therefore, the combined teachings of Fink/Barry will make the system of Barry not function according to its intended purpose.

In addition to the above reasons, claims 2-3, 6-19, 22-25, 27-28, 31-44, 45-49 are allowable at least based on their dependency.

In addition to the arguments related to claims 1 and 26 (which are equally valid here) claims 50 and 59 recite predicting progression of a biological process in an individual patient (or a general patient as in claim 50) under a plurality of treatment protocols, wherein the biological process could be related to healthy or diseased processes, the plurality of protocols including no treatment. There is no suggestion the combined teachings of Fink/Barry about predicting the progression of biological processes under several treatment protocols including no treatment.

Claims 51-52, 55-58 depend on claim 50 and are patentable at least for the same reasons.

Claims 60-65 are dependant on claim 59 and are patentable for the same reasons.

Claims 274, 296, 316 and 325 are method claims corresponding to (and containing similar limitations to) the system claims 1, 26, 50 and 59 and are patentable at least for the same reasons.

Claims 275-276, 279-294, 295 depend on claim 274 and are patentable for the same reasons.

Claims 296-298, 301-315 are dependent on claim 316 and are patentable for the same reasons.

Claims 315-318, and 321-324 are method claims corresponding to claim 316 and are patentable for the same reasons.

Claims 326-327 and 330-331 are dependent on claim 325 and are patentable for the same reasons.

Claims 234-246 relate to a system system for recommending an optimal treatment protocol for treating cancer using drugs, including chemotherapy, for an individual. Claims 234-246 recite increasingly further improvements in a specific cancer system model. Other than simply and most generally asserting that Barry mentions the use of their system for various diseases including cancer, there is not even a remote suggestion of a specific cancer system model as used in the present invention.

In section IV.D, the present Specification discusses a very specific cancer model. This model is claimed with increasing specificity in claims 234-246. There is believed to be ABSOLUTELY NO SUGGESTION in the combined teachings of

Barry/Fink regarding any aspects of the cancer system model disclosed in the present Specification (and claimed in claims 234-246).

Claims 248-261 correspond to a system for predicting the progression of cancer in an individual and contains limitation similar to claims 234-246. Therefore the arguments made above for claims 234-246 are equally valid.

Claims 262-273 are similar to claims 234-246, but relate to a general patient. Arguments discussed above in relation to claims 234-246 are equally valid for claims 234-246.

Claim 480-505 are method claims corresponding to the system claims 234-273, and therefore are patentable at least for the same reasons.

IV.C. Rejection of 1-65, 234-331, 466-509 under 35 U.S.C. § 103(a)based on Barry in view of Fink and Thalhammer-Rayero

In rejecting all the pending claims based on the prior art combination Berry/Fink/Thalhammer-Reyero, the Examiner has not shown clearly how Thalhammer-Reyero overcomes the deficiencies noted above in Barry and/or Fink. Therefore, he has not satisfied his burden of proof for establishing prima facie obviousness of the pending claims based on Berry/Fink/Thalhammer-Reyero.

While Thalhammer-Reyero is a very detailed modeling system, the building blocks for the model, the type of modeling suggested and the very few examples of actual models discussed are completely different from that of the present invention. Thalhammer-Reyero suggests a system that provides an environment for modeling

complex systems. The emphasis appears to be more on the knowledge representation and programming aspects of it as opposed to providing systems and methods for recommending an optimal treatment for a general patient or a specific individual.

Thalhammer-Reyero suggests processes represented as a combination of pools of entities, each such entity further including mathematical models and entities. A system is thereby represented as a network of pools and processes. There is nothing to suggest that such a network of pools and processes is a system model, as used in the present invention. The system model in the present invention is a mathematical model representing the overall bio-clinical scenario including relevant biological, clinical and pharmaceutical process. While the structure of the model building exercised and the associated graphical representation is discussed in great detail, there is nothing to suggest that clinical and pharmaceutical processes are contemplated.

To allegedly facilitate the building of the model, an information hierarchy is suggested. Several icons including phase icons, location icons, reservoir icons, process icons and entity icons are suggested by Thalhammer-Reyero. Phase icons represent discrete time compartments, location icons represent discrete space compartments, reservoir icons represent pools of entities, process icons represent processes in which entities participate and entity icons contain details about the entities themselves. In an object oriented representation scheme used BioObjects represent entities and BioModels represent phases and location icons.

The various subsections of the Summary section and the Detailed description do not appear to suggest the type of system model used in the present invention. In fact, they appear to teach away from it. In subsection A, it is emphasized that an important teaching is the method of representing complex systems. Subsection B emphasizes simulating the behavior of complex systems, recognizing a need to model quantities and transition states. Subsections C and D discusses further details of BioObjects and BioModels. Subsection E refers to combining inference rules with both qualitative and quantitative models. Subsection F discusses provisions for a the ability of an expert to change the knowledge. Subsection G discusses the incorporation of both space and time domains, while H discusses simulating pathways and cross talk between the pathways. Subsections I and J discuss Heterogeneous representation and quantitative as well as a semi-quantitative representation respectively. Subsection K discusses states as well as transition among states. Subsection K discusses iterative and interactive capabilities.

Clearly, bio-clinical scenario with an emphasis on clinical and pharmaceutical processes is not suggested.

Further, the examples, that show the implementation of the model building system of Thalhammer-Reyero do not suggest anything different. The example discussed in columns 14 and 15 relating to Oncostatin M does not appear to be suggesting an overall system model with overall bio-clinical scenario including

relevant biological, clinical and pharmaceutical process as used in the present invention.

Further it is clearly stated in 18:17-35 that:

> The bioPools representing synthetic agonists, antogonists or inhibitors such as drugs or toxic substances have a basal-concentration of 0, have no modeled inputs other than the user-entries..

Further, in relation to claims 1-25 and other claims related to individual patients, there is no teaching in Thalhammer-Reyero about modifying the system model using parameters specific to the individual. The Examiner is requested to specifically point out in Thalhammer-Reyero where this feature is suggested.

In addition, regarding claims related to the treatment of cancer, 234-273, and 466-505, the Examiner appears to be asserting that Thalhammer-Reyero suggests a method for modeling biological systems organized in discrete compartments. The Applicants respectfully submit that there is nothing in Thalhammer-Reyero to suggest that a cancer system model and a treatment of cancer is contemplated. Again the Examiner is requested to specifically point out where cancer and its treatment is suggested.

Regarding claim 234, there is no suggestion in Thalhammer-Reyero that the model is a cancer system model and there is no further suggestion regarding a plurality of treatment protocols using chemotherapy. Still further, there is no selector selecting optimal treatments.

Further, there are substantial differences between the cancer system model of the present invention and the modeling system suggested by Thalhammer-Reyero.

The detailed Description section, apart from discussing the knowledge representation aspects of the system, discusses several modes of operation. In the developer mode, object classes and methods are discussed. BioModel is described as a predefined object encapsulating bioObjects. One of the bioModel is a subclass called cell-BioModel. While compartments are discussed in general, this is very different from the compartments of the present invention. Just because, common terminology for cell states is used does not mean that the actual mathematical models are not patentably distinct. For that matter, G1, S, G2, M and Go are commonly used.

However, the present invention, at least as recited in claim 237, require that the compartments be further subdivided into sub-compartments with the ith sub-compartment representing cells of age I. Also, the cells entering a compartment always enter a first sub-compartment of the compartment. In Thalammer-Reyero there is no suggestion that the compartments are further divided into sub-compartments. Clearly, further refinements of the model claimed in claims 234-246 make the present invention and Thalhammer-Reyero even more patentably distinct.

Further, a skilled artisan would not have been motivated to combine the teachings of Thalhammer-Reyero with Berry/Fink because the combined system will not work or will require considerable modification to work. First, Thalhammer-

Reyero is clearly an object-oriented system with multiple interactions and network of biological entities. On the other hand Berry simply selects from a database of treatment protocols based on information about a patient. There is no interrelationship among entities as in Thalhammer-Reyero. Fink on the other hand is a strictly hierarchical biological model. Such a strict hierarchical model cannot work with the network of cross relationships as in Thalhammer-Reyero. Therefore, a skilled artisan would not have been motivated to combine the teachings of Fink, Berry and Thalhammer-Reyero.

Therefore all the pending claims should be allowed.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

a) IN THE CLAIMS:

The claims are amended as follows:

5. The system of claim 3 wherein said cell populations with at least one disease is one of cancer cells, and diseased bone-marrow cells including diseased Neutrophil cells and diseased [Thrompocyte] Thrombocyte cells.

8. The [method] system of claim 1 wherein, said parameters specific to the individual include one or more selected from a group consisting of parameters related to the biological process' dynamics, patient specific drug PK, PD and dynamics of dose-limiting host tissues.

9. The [method] system of claim 8, wherein said parameters related to biological process' dynamics comprise age, weight, gender, blood picture, desired length of treatment protocol, previous reaction to treatment, molecular markers, genetic markers, pathologic specifics and cytologic specifics.

246. The system of claim [231] 234 wherein, said parameters specific to the individual comprise parameters related to tumor dynamics, patient specific drug PK, and dynamics of dose-limiting host tissues.